EXHIBIT 9

EDITORIAL

Methadone and Ketamine: Boosting Benefits and Still More to Learn

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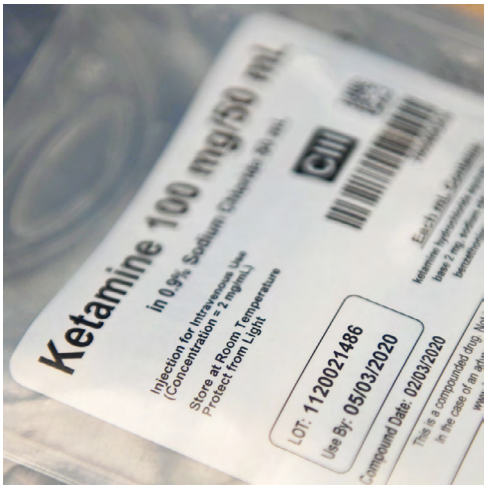
Methadone is a utilitarian opioid with multiple applications in anesthesiology, acute pain, cancer pain, sickle cell disease, and opioid use disorder, in both adults and children. Although methadone was only modestly popular after initial introduction to anesthesia practice in the early 1980s,[1] subsequent "reintroduction" more than 20 yr later[2] spurred growing use in the ensuing decade.[3] Multiple clinical studies have demonstrated the clinical benefits and therapeutic advantages of perioperative long-duration methadone compared with shorter-duration opioids, for both inpatient and outpatient surgery. Patients receiving a single intraoperative dose of methadone, compared with shorter-duration opioids, report less pain, use less opioid, and have greater satisfaction with pain relief. Moreover, these advantages seem to persist for weeks or months after surgery.[4,5] Indeed, methadone is aptly described as an "opioid-sparing opioid."



"Ketamine appears to have 'boosted' the effects of methadone…"

Compared with other opioids, less is known about methadone in the context of perioperative drug combinations. In this issue of Anesthesiology, Murphy *et al.*[6] report a clinical trial that compared the combination of methadone plus ketamine to methadone alone in patients undergoing elective spine surgery. One hundred thirty patients undergoing mainly single-level lumbar fusion received intraoperative methadone (0.2 mg/kg ideal body weight) and either placebo or ketamine ($0.3\ mg \cdot kg^{-1} \cdot h^{-1}$ intraoperatively, then $0.1\ mg \cdot kg^{-1} \cdot h^{-1}$ for the next 48 h), along with sevoflurane, propofol, and remifentanil. The primary outcome was intravenous hydromorphone use on postoperative day 1, and the hypothesis was that adding ketamine to methadone would result in less hydromorphone use. Secondary outcomes included pain scores, cumulative intravenous and oral opioid requirements, and patient satisfaction with pain management for the first 3 postoperative days.

The results were unambiguous and clinically meaningful. Median postoperative intravenous hydromorphone use was statistically less on day 1 after methadone/ketamine *versus* methadone alone (2.0 *vs.* 4.6 mg) and cumulatively over 72 h (2.7 *vs.* 5.8 mg). Postoperative oral opioid use after methadone/ketamine was also half that after methadone alone (11 *vs.* 20 tablets). Bolstering the significance of the differences in opioid requirements, pain scores at rest, with coughing, and with movement were significantly one-third lower (3 to 4 *vs.* 5 to 6) in the methadone/ketamine group at nearly every assessment time over 72 h. Adverse events (sedation, nausea, vomiting, dizziness, hallucinations, hypoxia, hypoventilation) were not different between groups. Thus, the addition of ketamine to methadone was highly effective, resulting in half the opioid use and one-third less pain compared with methadone alone.

The magnitude of these effects was unusually large, clinically relevant, and thought-provoking. Ketamine appears to have "boosted" the effects of methadone in a manner analogous to the "boosting" of antiretrovirals by coadministering low doses of ritonavir—a protease inhibitor with only modest effects when used alone.

The study by Murphy *et al.*[6] is remarkable for several reasons. First, it actually evaluated a simple, practical, multimodal anesthetic regimen with a design enabling the testing of a specific hypothesis, rather than testing a complex "bundle," which may inform on the aggregate but not the value of specific components. Multimodal analgesia is a contemporary centerpiece of the perioperative protocol banquet, and such protocols are widely espoused and often

Image: J. P. Rathmell.

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enthusiastically embraced. While perhaps sometimes beneficial, they are also insufficiently tested and are unfortunately often found less effective than believed or desired when they are finally formally evaluated.[7] Moreover, in addition to opioid consumption, the methadone–ketamine trial evaluated the important and patient-centric outcomes: pain and unwanted side effects. There has been a switch from trials emphasizing pain relief as a primary outcome, to quantifying opioid consumption as a goal unto itself as a primary or even sole outcome. This may reflect the ease, low expense, and objectivity of obtaining drug administration data (retrospective review of electronic medical records rather than hiring research staff to query patients about pain) or misattribution of the nation's opioid crisis to immediate postoperative opioid prescribing. Nevertheless, opioid sparing by itself is not likely meaningful to patients unless accompanied by improved patient-centric outcomes like better pain relief or the sparing of undesirable opioid-related side effects. Furthermore, the investigation by Murphy *et al.*[6] was well designed and meticulously conducted and reported—all at a private hospital. The point is that high-quality clinical research is not the exclusive province of tertiary care academic institutions—a message that we hope will be widely heard and heeded.

Second, the magnitude of the effect of adding ketamine to an opioid was substantially greater than commonly reported. Much enthusiasm attends to ketamine use, although enthusiasm may exceed reported benefits.[8] A review of the initial decades of ketamine use for postoperative pain across a range of surgical procedures found mixed evidence for and against better analgesia and opioid sparing,[9] a finding recapitulated a decade later.[10] The most recent comprehensive review,[11] encompassing 130 studies of various surgical procedures with more than 8,300 patients, evaluating ketamine given before, during, or after surgery (predominantly 0.12 to 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$) found that compared with placebo, postoperative opioid use over 48 h was less (median 54 *vs.* 67 mg), and pain at rest or with movement after 24 and 48 h was less (6 mm with movement on a 100-mm scale; median, 31 *vs.* 37 mm). Nevertheless, the 20% less opioid use and the 15 to 20% less pain were statistically significant but considered below the clinically important difference of 30%.[11] Evaluations focusing specifically on spine surgery found similarly marginal results. Ketamine addition had minimal or no effect on morphine use, pain, or opioid side effects after pediatric sciolosis surgery.[12,13] A meta-analysis found overall benefit but mixed evidence for better analgesia and opioid sparing with ketamine addition.[14] Interestingly, the one study (a statistical outlier) that showed the greatest benefit, and influenced the overall result, was with methadone. Most recently, a trial of intraoperative S-ketamine (0.5 mg/kg bolus plus 0.12 or 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion) *versus* placebo in spine surgery found no difference in the primary outcome of cumulative 48-h opioid consumption or in time-weighted average pain or pain after 3 and 24 months but greater sedation in the postanesthesia care unit.[11,15] Thus, the magnitude of the differences in opioid use and pain when combining ketamine with methadone, compared with methadone alone,[6] was far greater than when combining ketamine with other opioids. This contrast is remarkable.

The third notable aspect of the report by Murphy *et al.*[6] is, simply, the question of why, or how, did this happen? What is so different compared with the corpus of decades of previous ketamine studies? The most obvious answer is methadone. The results reported herein echo those of a previous small study in multilevel lumbar spine surgery using intraoperative methadone and methadone patient-controlled analgesia, plus either placebo or intraoperative ketamine infusion and ketamine added to patient-controlled analgesia.[16] Patients receiving ketamine used 79% less cumulative 48 h postoperative opioid, a very large treatment effect. What then is different about ketamine plus methadone compared with other opioids?

One simple explanation is the substantially slower elimination of methadone compared with other opioids, so that the additive or synergistic interaction lasts longer. However, most studies freely allow postoperative opioids, so that explanation seems unlikely. Another possible explanation is the pharmacologic difference between methadone and other opioids. Methadone is a μ-opioid receptor agonist and an *N*-methyl-D-asparate (NMDA) receptor antagonist, whereas most other opioids are essentially pure μ agonists. Some postulate that NMDA effects may contribute to the unique clinical properties of methadone. Nonetheless, clinical methadone concentrations after 0.2 mg/kg (less than 0.2 μM) are much lower than the IC_{50} or K_i of methadone for the NMDA receptor (3 to 10 μM).[17] Moreover, methadone analgesia is stereoselective, but NMDA receptor binding is not.[18] Thus, the unique methadone–ketamine interaction may not work through the NMDA receptor effects of methadone. Methadone also interacts with norepinephrine and serotonin reuptake systems at concentrations more closely resembling those achieved clinically.[19] Whether this mediates the methadone–ketamine interaction is unknown.

Ketamine is a noncompetitive NMDA receptor antagonist, and analgesia at subanesthetic concentrations is attributed to NMDA antagonism in the brain and spinal cord. Based on ketamine pharmacokinetics,[20] the bolus and infusion regimen used by Murphy *et al.*[6] would achieve plasma concentrations of approximately 0.4 μM, which is in the range of the IC_{50} or K_i for the NMDA receptor (0.2 to 1 μM),[21] and known analgesic concentrations (0.4 to 0.7 μM).[22] Perhaps the NMDA-specific effects of ketamine and methadone might be additive, but this appears unlikely based on the above calculations.

Another potential explanation is that analgesia from methadone alone was simply insufficient and was augmented by postoperative ketamine. This parsimonious explanation is certainly possible because the methadone

dose (0.2 mg/mg) was comparatively low (20 mg is a more conventional dose, particularly for spine surgery), as was evidenced by the need for additional intraoperative opioid (fentanyl, remifentanil, and hydromorphone). The influence of ketamine addition to a higher methadone dose, or perhaps the effect of a higher methadone dose alone, awaits exploration.

Another possibility explaining the ketamine–methadone advantage is the specific patient population and type of pain. Ketamine and methadone are believed to be more effective than other opioids for neuropathic pain, even if the clinical data are presently not compelling.[23,24] Neuropathic contributions to postoperative pain are poorly understood, although more than 13% of postoperative patients having a mix of surgeries had pain of a neuropathic nature,[25] and the incidence of preexisting neuropathic pain was nearly 50% in spine surgery patients.[26] The high prevalence of chronic postoperative neuropathic pain suggests that surgical nerve damage is common and may also contribute to immediate postoperative pain.[27] Interestingly, the ketamine–methadone combination appears synergistic in animal models of neuropathic pain and that synergy is greater than with other opioids.[28]

A separate process potentially explaining the effects of ketamine plus methadone for spinal surgery relates to preoperative opioid consumption and intraoperative remifentanil infusions. Patients in the trial by Murphy *et al.*[6] received approximately 3 mg of remifentanil. Intraoperative remifentanil in large doses is linked to increased postoperative pain and opioid requirements.[29] Remifentanil-induced hyperalgesia can be lessened by a simultaneous ketamine infusion.[30] Moreover, opioid-induced hyperalgesia is measurable in patients taking opioids for chronic pain,[31] and half of the patients in the methadone–ketamine study were taking preoperative opioids.[6] Thus, ketamine may have exerted part of its effects not by directly providing analgesia but indirectly by mitigating opioid (intraoperative remifentanil or chronic preoperative)–induced sensitization. Interestingly, methadone too may resolve opioid-induced hyperalgesia and reduce opioid requirements.[32] Thus, like ketamine, methadone could enhance postoperative pain control in part by reducing opioid-induced hyperalgesia, an effect not likely provided by other opioids.

What then have we learned? This was not just another ketamine-opioid trial. Spine surgery patients receiving ketamine plus 0.2 mg/kg methadone had less pain and used less opioid than those receiving 0.2 mg/kg methadone alone, an effect different than when combining ketamine with other opioids. Such methadone "boosting" with ketamine may be clinically useful, and we are also left with more questions than before. Are the effects pharmacokinetic, pharmacodynamic, direct (methadone analgesia), indirect (less opioid hyperalgesia), methadone dose-related, specific to spine surgery, or other? All are good and important questions to explore and answer.

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Competing Interests

Dr. Clark has a consulting agreement with Teikoku Pharma USA (San Jose, California). Dr. Kharasch declares no competing interests.

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